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Unusual association of diseases/symptoms

Neonatal thyrotoxicosis presenting as persistent pulmonary hypertension

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Summary

Neonatal hyperthyroidism is a rare condition caused either by transplacental passage of thyroid-stimulating immunoglobulins from a mother with Graves' disease or by activating mutations of the thyrotropin receptors and α-subunit of G-protein. The clinical features may vary. We report a case of neonatal thyrotoxicosis in an infant born to a mother with Graves' disease, who presented with cardiorespiratory failure and persistent pulmonary hypertension (PPHN). PPHN resolved with specific antithyroid treatment and extracorporeal membrane oxygenation was not required.

BACKGROUND

Neonatal thyrotoxicosis is a rare condition caused either by transplacental passage of the maternal thyroid-stimulating immunoglobulins (TSI) from a mother with Graves' diseases or by activating mutations of the thyrotropin receptors and α-subunit of G-protein.[1 2] We report a patient of neonatal thyrotoxicosis presenting with persistent pulmonary hypertension (PPHN) that required mechanical ventilation and inhaled nitric oxide (iNO) administration. Although hyperthyroidism has been associated with pulmonary hypertension among adults, to the best of our knowledge, there are only two reported cases of neonatal thyrotoxicosis presenting with PPHN.[3 4]

CASE PRESENTATION

A 9-days-old full-term male infant presented to his paediatrician's office with the complaint of rapid breathing for 1–2 days. He was born by caesarean section, had no complications after delivery and was discharged home with the mother on day 3 of life. A chest x-ray done at paediatrician's office showed significant cardiomegaly with normal-looking lung fields. He was then sent to our neonatal intensive care unit for further evaluation and management.

Initial physical examination was remarkable for tachypnoea, tachycardia and oxygen saturation of 80% in room air. The echocardiogram showed an increase in the right ventricle systolic pressure, dilatation of the right ventricle with moderate tricuspid regurgitation, and a bi-directional shunt at the foramen ovale. Based on the clinical presentation and echocardiogram findings, a diagnosis of PPHN was made. The patient required endotracheal intubation and mechanical ventilation with 100% FiO_2 on the day of admission. As his haemodynamic lability persisted, he was eventually started on iNO. He also developed poor peripheral perfusion and received multiple normal saline boluses (a total of 100 ml/kg), followed by dopamine and dobutamine continuous infusions.

Until this time, the medical team was not aware of the history of maternal Graves' disease and high T4 (thyroxine) and low thyroid-stimulating hormone (TSH) levels in the infant's newborn screen. It was discovered that the mother was diagnosed with Graves' disease 2 years ago and she was on propylthiouracil. Her last thyroid function tests prior to delivery were: TSH unknown, free T3 −7.0 pg/ml (normal: 2.3–4.2 pg/ml), free T4 −0.84 ng/dl (normal: 0.89–1.8 ng/dl) and TSI index −4.8 (normal <1.3). Free T4 was reported to be high throughout pregnancy.

The infant's free T4 levels were 6 and 10.5 ng/dl on day 5 and day 9 of life, respectively (normal 0.9–1.8 ng/dl). The TSI index was 1.5 (normal <1.3) when measured on day 10 of life. A diagnosis of neonatal thyrotoxicosis with possible thyroid storm was made.

INVESTIGATIONS

- T3-total: 135 ng/dl (normal range: 60–180 ng/dl)
- Free T4: 10.5 ng/dl (normal range: 0.9–1.8 ng/dl)
- TSH level: 0.017 mIU/l (normal range: 3–20 mIU/l)
- C-reactive protein: 2.83 mg/l (normal range: 0–9 mg/l)
- Blood culture: no growth.

DIFFERENTIAL DIAGNOSIS

- Congenital heart disease
- Sepsis of newborn.

TREATMENT

The treatment of the infant was started with methimazole, Lugol's iodine solution, esmolol drip and intravenous

hydrocortisone. Within the next 1–2 days, we were able to wean his ventilatory support and eventually he was extubated. Afterwards, he maintained good saturations (>95%) on room air. After normal thyroid function tests on day 6 of hospitalisation, he was discharged home on methimazole and propranolol with a plan to follow up in the pediatric-endocrinology clinic.

OUTCOME AND FOLLOW-UP

At the follow-up visit to the endocrinology clinic 14 days after discharge, he was found to be doing well with a normal heart rate and appropriate weight gain. Propranolol and methimazole were gradually tapered and eventually discontinued at 2½ months of age. Repeat thyroid function tests at 2½ and 3 months of age were all normal.

DISCUSSION

Neonatal thyrotoxicosis may have a varied clinical presentation, ranging from a totally asymptomatic healthy newborn to the one with severe thyroid storm causing cardiopulmonary instability.[4–6] Increased thyroid hormone levels are associated with an increase in the total blood volume, heart rate and cardiac contractility, and a decrease in total systemic vascular resistance, all of which result in a hyperdynamic circulatory state and an increased workload for the heart. These cardiovascular changes may be mediated by thyroid hormone-induced increase in calcium ATPase activity, sarcolemmic sodium transport and calcium influx.[7]

Although hyperthyroidism has been associated with pulmonary hypertension in adults,[8] neonatal thyrotoxicosis presenting with PPHN is extremely rare, and to the best of our knowledge, there are only two such cases reported in the literature to date. Markham and Stevens[3] reported an infant born at 34 weeks gestation, who developed neonatal thyrotoxicosis with PPHN and was managed with propranolol and oxygen. Oden and Cheifetz[4] described the second such infant, who was born at 36 weeks gestation and developed severe PPHN associated with neonatal thyrotoxicosis necessitating extra-corporeal membrane oxygenation. In both the cases, the first chest x-ray after birth showed pneumothorax, and unlike our patient, signs and symptoms of neonatal thyrotoxicosis were present immediately after birth. Interestingly, in all these infants including the one reported by us, treating hyperthyroidism resulted in complete resolution of symptoms.

The exact reason for the development of pulmonary hypertension in hyperthyroidism is unclear. Proposed mechanisms include high cardiac output-induced endothelial injury, impaired production and increased metabolism of intrinsic pulmonary vasodilating substances (NO, prostacyclin, etc), and decreased clearance of pulmonary artery vasoconstrictors (serotonin, endothelin-1 and thromboxane).[4 8]

Once the diagnosis of neonatal hyperthyroidism is confirmed by clinical and biochemical evaluation, prompt treatment should be started with a combination of the antithyroid drug methimazole and a β-adrenergic blocker such as propranolol to control neuromuscular and cardiovascular hyperactivity.[9] Continuous intravenous infusion with esmolol (another β-adrenergic blocker) may be required in the initial phase in infants presenting with thyroid storm. Iodine (Lugol's solution or potassium iodide) inhibits thyroid hormone release and may be used in infants whose symptoms are not controlled with a combination of methimazole and a β-adrenergic blocker.[9] Hydrocortisone may benefit extremely sick neonates not only by its anti-inflammatory actions, but also by the ability to inhibit thyroid hormone secretion and decrease the peripheral conversion of T4 to triiodothyronine.[9]

Learning points

- Neonatal hyperthyroidism is a rare condition, caused most commonly by transplacental passage of thyroid-stimulating immunoglobulins from a mother with Graves' disease.
- Neonatal thyrotoxicosis should be considered in infants with unexplained persistent pulmonary hypertension.
- Effective treatment of hyperthyroidism with a combination therapy leads to complete resolution of symptoms in most cases.

Competing interests None.

Patient consent Obtained.

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